



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Patrizia Caldirola et al. Art Unit : 1624
Serial No. : 10/037,110 Examiner : Thomas C. McKenzie
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Title : NOVEL COMPOUNDS, THEIR USE AND PREPARATION

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Commissioner for Patents
P.O. Box 1450
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REPLY TO ADVISORY ACTION OF JULY 26, 2004

This Reply is responsive to the Advisory Action dated July 26, 2004 and is being filed concurrently with a Request for Examination under 37 C.F.R. § 1.114.

Status of the Claims

Claims 1-18, 22-25, 28-30, 32-34, 36-44, 46-56, and 59-61 are pending in the application. Applicants acknowledge that the Examiner has allowed claim 32; withdrawn the rejection of claims 24, 25, 34, 35, 44, and 54-57 under 35 U.S.C. § 112, second paragraph; and withdrawn the rejection of claims 24, 25, 27, 44, and 54-58 under 35 U.S.C. § 112, first paragraph.

Claims 1-5, 11-14, 18, 22-24, 28-30, 33, 34, 36-40, 44, 46-49, 54, 55, 59, and 60 remain rejected (this rejection will be addressed in the discussion below). The Examiner has also objected to claims 6-10, 15-17, 25, 41-43, 50-54, 56, and 61, presumably, in each case, for being dependent upon a rejected base claim. Applicants note that claim 54 is listed as being both a rejected and objected to claim. Applicants respectfully request clarification of the status of claim 54.

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Rejection under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 1-5, 11-14, 18, 22-24, 28-30, 33, 34, 36-40, 44, 46-49, 54, 55, 59, and 60 under 35 U.S.C. § 103(a) as being unpatentable over Isaac et al., *Bioorganic and Medicinal Chemistry Letters* **2000**, 1719 ("Isaac"). The Examiner summarized Applicants' previous arguments (i.e., set forth in the Reply filed on July 13, 2004) concerning this rejection as follows:

Applicants argue that there are no per se rules concerning the obviousness of position isomers and that there is no teaching or motivation supplied in Isaac ... to switch the point of attachment to the claimed positions 4 or 5 from the taught point of attachment at position 6 (Advisory Action, continuation sheet (PTOL-303), lines 4-7).

The Examiner has stated that the aforementioned arguments are "not persuasive" (Advisory Action, continuation sheet (PTOL-303), line 7). Specifically, the Examiner argued:

- (i) "[f]irstly, if it were both teaching and motivation supplied by the reference, then it would be anticipation not an obviousness rejection" (Advisory Action, continuation sheet (PTOL-303), lines 7-8); and
- (ii) "[s]econdly, the medicinal chemist routinely prepares isomers of active compounds as a part of routine experimentation. The motivation is to explore the SAR, to prepare more active compounds, and at times to work around the prior art" (Advisory Action, continuation sheet (PTOL-303), lines 8-10).

Finally, the Examiner has cited a number of cases in support of the foregoing rejection (see Advisory Action, continuation sheet (PTOL-303), lines 10-21).

Applicants respectfully disagree with the Examiner's analysis and submit that claims 1-5, 11-14, 18, 22-24, 28-30, 33, 34, 36-40, 44, 46-49, 54, 55, 59, and 60 are patentable over Isaac for any of several reasons, which are summarized here and will be discussed in more detail below.

First, Applicants reiterate that there is no legal precedent for *per se* rules of obviousness, that it is improper to extract such rules from the case law, and that it is legally incorrect to apply *per se* rules of obviousness.

Second, the prior art fails to provide reason or motivation to make Applicants' compounds for at least the following reasons. A showing of motivation cannot be based on broad conclusory statements lacking evidentiary support. There is no evidence presented that the prior art suggests the specific molecular modification needed to arrive at Applicants' compounds. The Examiner's analysis of obviousness is essentially limited to a discussion of how the prior art compounds could be modified. The mere fact that prior art teachings could be modified is not probative to the question of obviousness.

Third, structural similarity in and of itself does not give rise to obviousness. The presumption of obviousness created by the existence of a structurally similar prior art compound is based, in part, on the expectation that structurally similar compounds will have similar properties. Such an expectation is not justified here.

There are no per se rules of obviousness

Before addressing of the specific points raised by the Examiner in the Advisory Action, Applicants again wish to clarify that **there are no per se rules of obviousness of any kind, let alone per se rules "concerning the obviousness of position isomers."** This assertion is not merely argumentation, but a fact of law:

We once again hold today that our precedents do not establish any per se rules of obviousness, just as those precedents themselves expressly declined to create such rules. Any conflicts as may be perceived to exist derive from an impermissible effort to extract per se rules from decisions that disavow precisely such extraction *In re Ochiai* 37 USPQ2d 1127, 1133 (Fed. Cir. 1995) (underline emphasis added; italics in original).

The obviousness inquiry under 35 U.S.C. § 103(a) is "highly fact-specific by design." *Ochiai* at 1131. "Whether invention exists over prior art isomers and homologues is a question

to be decided in each case.” *In re Henze* 85 USPQ 261, 264 (CCPA 1950). The Examiner has cited a line of cases where a claimed compound or genus was held as being obvious over a prior art position isomer. These cited cases, however, do not in and of themselves establish or imply that there exists any general obviousness rule that a compound claim is obvious if the prior art discloses a position isomer thereof. As the Federal Circuit explained in *Ochiai*:

...the examiner incorrectly drew from *Durden*, a case turning on specific facts, a general obviousness rule: namely, that a process claim is obvious if the prior art references disclose the same general process using similar starting materials.⁵ No such per se rule exists. Mere citation of *Durden*, *Albertson*, or any other case as a basis for rejecting process claims that differ from the prior art by their use of different starting materials is improper, as it sidesteps the fact-intensive inquiry mandated by section 103. In other words, there are not ‘*Durden* obviousness rejections’ or ‘*Albertson* obviousness rejections,’ but rather only section 103 obviousness rejections. *Ochiai* at 1131 (italics in original).

In a non-precedential opinion, the United States Patent and Trademark Office (USPTO) Board of Patent Appeals and Interferences (“the Board”) recently applied the holdings of *Ochiai* specifically to the question of obviousness of a claimed stereoisomer in view of the disclosure of a different stereoisomer in the prior art. *Ex Parte Bonfils* 64 USPQ2d 1456 (U.S. Patent and Trademark Office Board of Patent Appeals and Interferences, 2002, Non-precedential).

In *Bonfils*, the claims were directed to steroids having a particular absolute configuration about each of carbon atoms 8, 9, 13, and 14 of the steroid skeleton. The examiner in *Bonfils* rejected the claims as being obvious over two prior art references that disclosed steroids having the same constituent atoms and connectivity as the claimed compounds, but the opposite absolute configuration about each of carbon atoms 8, 9, 13, and 14. In other words, the claimed compounds and prior art compounds were related to one another as stereoisomers, i.e., isomers that differ only in the three-dimensional arrangement of substituents about one or more atoms, but otherwise have an identical chemical constituency (compare positional isomers, which do have different connectivity).

The Board reversed and expressed dissatisfaction with the evidence relied upon by the examiner for establishing the *prima facie* case of obviousness and the Board offered a pointed admonition against the use of *per se* rules when applying 35 U.S.C. § 103(a) to claims directed to chemical compounds:

The only fact relied on by the examiner in this appeal is that RU-1 discloses a stereoisomer of the claimed compounds. ... While a single disclosed chemical structure or formula might suffice as the *sole* evidence of unpatentability in a rejection under 35 U.S.C. § 102 for anticipation, such will rarely, if ever, suffice as substantial evidence of obviousness under § 103(a). This is because the examiner must explain why the differences would have been obvious, and the explanation must be supported by the evidence in the record. ... the examiner appears to have relied on a *per se* rule that a stereoisomer is obvious in view of a disclosure of another stereoisomer in the prior art. (Answer at 4.) This is error. Ochiai at 1572, 37 USPQ2d at 1133 ('reliance on *per se* rules of obviousness is legally incorrect and must cease.') *Ex Parte Bonfils* 64 USPQ2d 1456, 1461 (U.S. Patent and Trademark Office Board of Patent Appeals and Interferences, 2002, Non-precedential; underline emphasis added, italics in original).

The views expressed in *Bonfils* affirm that there are no *per se* rules of obviousness even where the structural difference between the claimed and prior art compounds is indeed quite subtle—a matter of stereoisomerism.

Finally, it is noted here that the Board in *Bonfils* did not agree that *In re Deuel* 34 USPQ2d 1210 (Fed. Cir. 1995) supported the examiner's grounds for the above-mentioned obviousness rejection (*Bonfils* at 1461; *Deuel* was also cited by the Examiner in the present Advisory Action in support of the outstanding obviousness rejection). More will be said about *Deuel* in the following discussion concerning the motivation prong of the *prima facie* case.

Prior art does not provide reason or motivation to make claimed compounds

Background

The foregoing rejection is based on a single reference (Isaac). As discussed in detail elsewhere in the record, it is an indisputable fact that Isaac is wholly deficient of any teaching or

suggestion to make the modification needed to arrive at Applicants' claimed compounds, i.e., moving the heterocyclic moiety from the 6-position of the indole ring, as taught in Isaac, to the 4- and/or 5-position of the indole ring, as discovered by Applicants.

In the previous Office Actions (dated April 28, 2003 and January 28, 2004), the Examiner has not disputed the absence in Isaac of any suggestion or motivation to vary the point of attachment of the heterocyclyl moiety, much less any suggestion or motivation to attach the heterocyclyl moiety to the C-4 or C-5 position of the indole ring. The Examiner has made no assertions to the contrary here. With regard to the Examiner's comments at lines 7-8 of the Advisory Action continuation sheet (PTOL-303), Applicants are aware of the legal distinction between 35 U.S.C. § 102 and 35 U.S.C. § 103. Applicants' statement that Isaac does not teach or suggest the aforementioned modification simply underscores the plain fact that there is no disclosure in Isaac, explicit or implicit, that would motivate a person of ordinary skill in the art to make the aforementioned modification.

The Examiner has previously argued that compounds with a heterocyclyl moiety attached at the C-4 or C-5 position of the indole ring are "*per se* ring obvious position isomers" of the compounds in Isaac. The Examiner has also alleged that no secondary teaching is required because varying the point of attachment of the heterocyclyl moiety to the indole ring would be merely "routine" for a "medicinal chemist."

Summary of Examiner's arguments for maintaining the rejection

For the record, the foregoing rejection remains based on the same single reference, Isaac.

The Examiner has argued in this Advisory Action that the "medicinal chemist routinely prepares isomers of active compounds" and the "motivation is to explore the SAR, to prepare more active compounds, and at times to work around the prior art" (*vide supra*). The Examiner has also quoted the following passage from *Ex Parte Engelhardt* 208 USPQ 343 (POBA 1980), presumably in support of this assertion:

...position isomerism has been used as a tool to obtain new and useful drugs (see Advisory Action, continuation sheet (PTOL-303), lines 10-11, quoting *Engelhardt* at 349).

Applicants' Rebuttal

Summary

Applicants respectfully disagree. and submit that the prior art fails to provide reason or motivation to make Applicants' compounds for any of the following reasons. First, a showing of motivation cannot be based on broad conclusory statements lacking evidentiary support. Second, there is no evidence presented that the prior art suggests the specific molecular modification needed to arrive at Applicants' compounds. Third, the Examiner's analysis of obviousness is essentially limited to a discussion of how the prior art could be modified. Mere fact that prior art teachings could be modified is not probative to the question of obviousness.

Legal standards for showing of motivation to modify prior art teachings not met

"Even when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference. *See B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1582, 37 USPQ2d 1314, 1318 (Fed. Cir. 1996)." *In re Kotzab* 55 USPQ2d 1313, 1316-1317 (Fed. Cir. 2000) (underline emphasis added, italics in original). "The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the

problem to be solved. *See Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617. In addition, the teaching, motivation or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references.” *Kotzab* at 1317.

While the locus of the suggestion or motivation need not be expressly stated in the prior art reference, the Courts have held that an implicit showing of suggestion or motivation in the prior art must nevertheless be supported by evidentiary findings of fact, and that broad conclusory statements do not constitute such evidence of a showing of suggestion or motivation:

Whether the Board relies on an express or an implicit showing, it must provide particular findings related thereto. *See Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617. *Kotzab* at 1317.

Broad conclusory statements standing alone are not ‘evidence.’ *Id.* *Kotzab* at 1317.

Broad conclusory statements, regarding the teaching of multiple references, standing alone are not ‘evidence.’ *E.g.*, *McElmurry v. Arkansas Power & Light Co.*, 995 F.2d 1576, 1578, 27 USPQ2d 1129, 1131 (Fed. Cir. 1993) (‘Mere denials and conclusory statements, however, are not sufficient to establish a genuine issue of material fact’); ... *In re Dembiczak* 50 USPQ 1614, 1617 (Fed. Cir. 1999).

In *In re Lee* 61 USPQ2d 1430 (Fed. Cir. 2002), the Federal Circuit reaffirmed that an absence of suggestion or motivation in the express teachings of the prior art **cannot** be cured by conclusory statements regarding “basic knowledge” or “common sense.”

This factual question of motivation is material to patentability, and could not be resolved on subjective belief and unknown authority. ... Conclusory statements such as those here provided do not fulfill the agency’s obligation. This court explained in *Zurko*, 258 F.3d at 1385, 59 USPQ2d at 1697, that ‘deficiencies of the cited references cannot be remedied by the Board’s general conclusions about what is ‘basic knowledge’ or ‘common sense.’’ ... ‘Common knowledge or common sense,’ even if assumed to derive from the agency’s expertise, do not substitute for authority when the law requires authority. *See Allentown Mack*, 522 U.S. at 376 ... *Lee* at 1434-1435 (underline emphasis added, italics in original).

See also *In re Thrift* 63 USPQ2d 2002, 2006 (Fed. Cir. 2002) (“Recently, in *In re Lee*... we held that the Board’s reliance on ‘common knowledge and common sense’ did not fulfill the agency’s obligation to cite references to support its conclusions.”).

As discussed elsewhere, Isaac, the single prior art reference relied upon in the present rejection, is indisputably deficient in any suggestion or motivation to modify the teachings of Isaac to arrive at Applicants’ claimed compounds, namely moving the heterocyclic moiety from the 6-position of the indole ring to the 4- and/or 5-position of the indole ring. The Examiner has attempted to cure this deficiency by asserting that the motivation to move the heterocyclic moiety from the 6-position of the indole ring to the 4- and/or 5-position of the indole ring is implicit (since it is not present in Isaac) from the basic or common knowledge in the art of medicinal chemistry.

However, the Examiner’s implicit showing of motivation merely consists of (unduly) broad conclusory statements: “the medicinal chemist routinely prepares isomers of active compounds as a part of routine experimentation” (which is unsubstantiated); “[t]he motivation is to explore the SAR, to prepare more active compounds,” (which is both unsubstantiated and at best speculative) and “at times to work around the prior art” (which is pure conjecture). Moreover, these statements are of unknown authority as the Examiner has provided no secondary teaching or any other evidence in support of them. As such, The Examiner has appeared to rely only upon what he believes to be common or basic knowledge in the art of medicinal chemistry to establish a showing of motivation.

While Engelhardt makes a passing reference to “position isomerism,” *Engelhardt* does not say, for example, that a “medicinal chemist routinely prepares isomers of active compounds.” The sentence immediately preceding the one quoted by the Examiner reads as follows:

If functional groups capable of withdrawing or repelling electrons are located in the chain or ring of a biologically active compound, transfer of such groups to other positions in which their electronic effects are lessened or enhanced may alter the biological activity of the modified compound (*Engelhardt* at 349, emphasis added).

Here, *Engelhardt* simply states that moving an electron withdrawing/donating group to “other positions” of a chain or ring of a biologically active compound (*nb.* no specific ring or specific position is disclosed by *Engelhardt*) may alter biological activity of the modified compound. Any *dicta* that a person of ordinary skill in the art (the legal standard here and who need not necessarily be “a medicinal chemist”) routinely performs this modification is absent in *Engelhardt*. Moreover, there is no evidence or rule disclosed or suggested in *Engelhardt* that the biological activity of an active compound is necessarily connected and/or variable with the electronic properties of a particular ring or chain of the active compound.

In any event, mere conclusory statements about what is common or basic knowledge in the prior art, without evidence in support thereto, do not constitute evidence for showing motivation or suggestion to modify the teachings of a prior art reference. The Examiner's showing of motivation to modify the teachings of Isaac to arrive at Applicants' claimed compounds therefore does not meet the legal standards set forth in the relevant case law. The Examiner has erred because reliance on self-asserted common knowledge does not meet the Office's obligation provide particular findings of fact related thereto.

Prior art must suggest the specific molecular modification

The suggestion or motivation to modify teachings of the prior art must be **specific**:

The need for specificity pervades this authority. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) ('particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components in the manner claimed')" (*Lee* at 1433).

[T]here must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant. (*Kotzab* at 1316).

The showing of a motivation to combine must be clear and particular, and it must be supported by actual evidence. *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). (*Teleflex Inc. v. Ficosa North America Corp.* 63 USPQ 2d 1374, 1387 (Fed. Cir. 2002)).

Turning to the more specific question of obviousness of a claimed chemical compound, the motivation or suggestion to modify the prior art teachings must be specific with regard to the chemical modification needed to arrive at the claimed compounds. *In re Deuel* 34 USPQ2d 1210 (Fed. Cir. 1995).

The Federal Circuit in *Deuel* reaffirmed the requirements for establishing *prima facie* obviousness of chemical compounds. The Court explained that while known compounds may suggest some categorically similar compounds (e.g., homologs, isomers), the question of obviousness turned on whether the prior art would have suggested the “specific molecular modification” necessary to arrive at the claimed compound:

Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs ... Similarly, a known compound may suggest its analogs or isomers, either geometric isomers (cis v. trans) or position isomers (e.g., ortho v. para).

In all of these cases, however, the prior art teaches a specific, structurally-definable compound and the question becomes whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention. See *In re Jones*, 958 F.2d 347, 351, 21 USPQ2d 1941, 1944 (Fed. Cir. 1992); *In re Dillon*, 191 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc) (‘structural similarity between claimed and prior art subject matter, ... where prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness’), ... *In re Grabiak*, 769 F.2d 729, 731-2, 226 USPQ 870, 872 (Fed. Cir. 1985) (‘[I]n the case before us there must be adequate support in the prior art for the [prior art] ester/[claimed] thioester change in structure, in order to complete the PTO’s prima facie case and shift the burden of going forward to the applicant.’) *In re Lalu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) (‘The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.’) *Deuel* at 1214, 1215 (underline emphasis added, italics in original).

Thus, a *prima facie* case of obviousness is established for a chemical composition where there is structural similarity between the claimed and reference compounds and where the prior art gives reason or motivation to make the claimed compounds. With regard to the motivation prong of the *prima facie* case, the prior art must suggest the specific molecular modification—not modification generally-- needed to arrive at the claimed compounds.

The Examiner's assertions are but mere generalizations that certainly do not in any way identify the specific molecular modification needed to arrive at Applicants' claimed compounds. At best, the Examiner's showing of motivation, which as discussed elsewhere is of unknown authority, says only something about the nature of the modification, but nothing more specific than that. Recall that excluding the 6-position, there are a total of six other nonequivalent, substitutable positions on the indole ring. The Examiner has provided no evidence to support the assertion that the prior art, with or without knowledge of the Isaac compounds, would have specifically suggested making the 4- and/or 5-substituted indoles discovered and claimed by Applicants. Again, as reaffirmed in *Lee*, findings must be made as to the reason a person of ordinary skill in the art, with no knowledge of Applicants' claimed invention, would have been motivated to specifically make Applicants' claimed compounds.

Prior art must suggest the desirability of modifying the teaching of the prior art

In view of the foregoing discussion, the Examiner's showing of motivation effectively amounts to nothing more than saying that the Isaac compounds could be modified to arrive at Applicants' claimed compounds.

However, it is well established that a claimed invention cannot be made obvious merely because the prior art could be modified; rather the prior art must suggest the desirability of making the modification. *In re Gordon* 221 USPQ 1125 (Fed. Cir. 1984). In *Gordon*, the appealed claims were directed to was a blood filter assembly having openings at the bottom of the assembly for both entry (inlet) and discharge of blood (outlet).

The examiner rejected the claims as being obvious over a single reference, which disclosed a liquid strainer for removing dirt and water from gasoline. In contrast to Gordon's assembly, the inlet and outlet ports of the prior art strainer were located at the top of the device. The USPTO Board of Appeals affirmed the rejection reasoning as follows:

...it would have been obvious to turn the French [*sic.*, the prior art] device upside down to have both the inlet and outlet at the bottom, rather than at the top (Gordon at 1127).

The Court reversed, stating in its analysis:

The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification (Gordon at 1127).

Thus, Gordon establishes that the mere assertion that a prior art teaching could be modified is of essentially no probative value in the obviousness inquiry under 35 U.S.C. 103(a).

Applicants do not dispute that position isomerism is a modification used in the drug discovery process. However, whether a person of ordinary skill in the art would be motivated to make a position isomer of an active compound is highly case-dependent (see, e.g., discussion elsewhere regarding Engelhardt). It is Applicants' position that there is simply nothing in the evidence of record that suggests the desirability of making a position isomer of any kind, let alone a 4- and/or 5-substituted position isomer as discovered by Applicants. What little evidence there is concerning this point, namely Isaac, would not motivate a person of ordinary skill to make this modification because Isaac appeared to vary nearly every parameter (e.g., the nature of the aryl sulfonyl moiety (i.e., "Ar") and the nitrogen content and ring size (i.e., "n") of the exclusively bicyclic heterocyclyl moiety) but the location of the heterocyclic moiety at position 6 in his already relatively potent compounds. In any event, mere fact that prior art teachings could be modified is not probative to the question of patentability under 35 U.S.C. § 103.

Conclusion

Applicants submit the motivation or suggestion to move the heterocyclic moiety from the 6-position of the indole ring to the 4- and/or 5-position of the indole ring is found only in Applicants' Specification. For the reasons set forth above, the Examiner has failed to establish that a person of ordinary skill in the art would have been motivated to make Applicants' claimed compounds and therefore the *prima facie* case of obviousness is incomplete.

Structural similarity in and of itself does not give rise to obviousness

"[I]t is not structural similarity alone that gives rise to obviousness, but the concomitant assumption that the structurally similar compounds will have like properties." *Ex Parte Chwang* 231 USPQ 751, 752 (Bd. Pat. App. & Int'f 1986).

Terms such as "positional isomer" infer that one or more similarities (e.g., in structure and/or properties) exist among a particular family of positional isomers. However, there also exists differences as well as similarities among compounds grouped according to a structural classification system. As the Court of Customs and Patent Appeals (CCPA) explained in *In re Mills* 126 USPQ 513 (CCPA 1960) with regard to homology:

[H]omology provides for the chemist a convenient system of structural classification; inherent in that system are differences as well as similarities in properties and reactions of members of any given homologous series; *Mills* at 514.

As discussed in detail elsewhere in the record, one of skill in the art would recognize that moving the heterocyclyl radical from C-6 to C-4 or C-5 would result in compounds clearly having significantly different shapes, dipole moments, etc. Accordingly, a person of skill in the art would not necessarily conclude that the C-6 and C-4 or C-5 compounds would have the same properties, i.e., it is reasonable to conclude that they would in fact have different properties.

Applicants again submit that this conclusion is borne out in the water solubility data included with the previously filed response.

The Examiner has provided no evidence to establish why a C-6 substituted indole compound would necessarily be expected to function similarly to a C-4 or C-5 substituted indolyl compound. E.g., in *In re Dillon* 16 USPQ2d 1897 (Fed. Cir. 1990), fuel compositions containing tetraorthoesters that reduced soot emissions were held as being obvious over prior art fuel compositions containing triorthoesters for the purpose of dewatering fuels. Among the evidence that was considered were secondary references, which provided evidence of equivalence in properties between tetraorthoesters and triorthoesters (specifically, the references taught that both tetraorthoesters and triorthoesters functioned similarly as water scavenger agents in hydraulic fluids). Even in the cases cited by the Examiner in the Advisory Action (e.g., *In re Jones* 74 USPQ 152 (CCPA), *In re Mehta* 146 USPQ 284 (CCPA 1965)), at least one secondary reference was provided by the USPTO that suggested some degree of equivalence between the claimed compounds and prior art position isomers.

Given the structural attributes of the indole skeleton and given that drug-receptor binding is highly sensitive to substrate molecular geometry, one of skill in the art would not necessarily have the expectation that the C-4/C-5 isomers would have the same properties as the C-6 positional isomer absent evidence to the contrary.

Applicant : Patrizia Caldirola et al.
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Enclosed is a \$2,160 check for the Five-Month Petition for Extension of Time fee.
Please apply any other charges or credits to deposit account 06-1050, referencing Attorney
Docket No.: 13425-052001.

Respectfully submitted,

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Date: February 11, 2005

FOR

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